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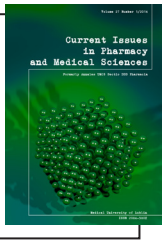

Review on analgesic effect of co-administrated ibuprofen and caffeine

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ABSTRACT

Pain is a symptom of many diseases and significantly affects the quality of life, so researchers are constantly seeking new substances to be used as analgesics. Other, easier way is to combine already known drugs which cause synergistic effects greater than additive, so that probability of drug-specific side effects can be reduced. Researchers showed that caffeine can be an effective analgesic adjuvant enhancing antinociceptive effect of ibuprofen in animals and humans. By using modern drug technology methods tablets containing well-soluble ibuprofen salt and caffeine can be easily prepared. Thanks to that combination, the therapeutic dose of ibuprofen can be lowered and the side effects may be reduced.

PAIN

Pain accompanies a number of diseases and is an issue that every person experiences. It is subjective and it is caused by stimulation of nerve endings [38]. Even mild or moderate pain can affect the quality of life. Analgesic ladder proposed by World Health Organization (WHO) is useful tool in the treatment of pain. There are three steps in that ladder, when pain control in not achieved it is recommended to use drug from the next step. First step consist of non-opioids adjuvants, next enclose weak opioids and drugs from the first step and the last step includes strong opioids with non-opioids [39]. Non-steroidal ant-inflammatory drugs (NSAIDs) from the first step are frequently used in pharmacotherapy of moderate intensity pain. Unfortunately, with increasing doses, NSAIDs (e.g. Ibuprofen) show significant side effects such as nausea, vomiting, headache or stomach ulcers [26]. Therefore, new analgesics with fewer side effects are sought. Also, doses of the active substances which are already used can be reduced by adding substances showing synergistic activity such as aspirin along with caffeine [22, 24].

CAFFEINE

Caffeine [Fig. 1] is an alkaloid present in coffee, tea, coca-cola beverages and chocolate [37]. The content of caffeine in selected products is shown in Table 1. Maximum plasma concentration after oral administration is observed between 30 minutes and 2 hours with caffeine bioavailability approaching 100%. Also, it is highly soluble in water and non-polar organic solvents [37]. Caffeine is also easily absorbed through the skin, while rectal administration is not used, because in that way caffeine is absorbed slowly and erratic. Low concentrations of caffeine can be present in breast milk and cross through placenta. It is metabolized almost completely in the liver and excreted in the urine in the form of metabolites. In adults half-lives elimination is about 3-7 hours. It is used as a mild stimulant in the doses of 50-100 mg, maximum 200 mg, no often than every 3 hours. In children, caffeine is used in the treatment of neonatal apnoea of prematurity in the doses of 10 mg/kg orally or by intravenous diffusion [26].

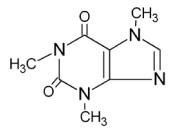

Figure 1. The chemical structure of caffeine

Caffeine has little or no analgesic effect when it is administrated alone, e.g. 130 mg of caffeine did not provide better pain relief than placebo [15]. However, it is often added to aspirin, codeine or paracetamol to increase their analgesic effect [4, 33]. That effect can be observed only when at least 100 mg of caffeine is used [27]. Despite the fact that there were numerous studies trying to find out how caffeine

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increases the antinociceptive effect of NSAIDs and there was much evidence that caffeine increased analgesic effects, the action mechanism is still not known [23, 33].

Caffeine can stimulate the central nervous system, reduce fatigue, stimulate mental activity, improve athletic performance, endurance, and reduce errors caused by workers because of tiredness [5, 8, 26]. On the other hand, high doses of caffeine can affect coordination, which leads to a poorer than expected athletic performance [36]. The physical dependence and tolerance can occur after a long-term consumption of caffeine [18, 29]. The tolerance increases especially for the stimulating effect, which causes people to take larger doses of caffeine [16]. Caffeine is an antagonist of adenosine receptors, because it has the molecular structure similar to adenosine. Therefore, it is capable of binding to the adenosine receptor within the cells, but it does not activate it [14].

Table 1. Content of caffeine in some drugs and food products [3, 6]

Product	Serving size	Caffeine per serving [mg]
Regular caffeine tablet	1 tablet	100
Extra strong caffeine tablet	1 tablet	200
Excedrin tablet	1 tablet	65
Coffee	250 ml	140-210
Tea	250 ml	30-100
Coca cola classic	250 ml	24
Energy drink	250 ml	80

IBUPROFEN

Ibuprofen [Fig. 2] is a widely used analgesic and antinflammatory drug. Its pharmacokinetics parameters are: elimination half time ($t_{1/2}$) = 2.2 h, terminal disposition rate constant (β) = 0.315 h^{-1}, apparent volume of distribution (V_d) = 0.1 l/kg, fraction of unchanged drug excreted in urine (F_{el}) = 0.01, fraction of drug absorbed (f) = 1.0, extent of protein binding in plasma (EPB) = 99%, therapeutic range (Ther. Range) = 5-50 μg/ml, doses (d) = 200-600 mg, time to reach the peak upon extravascular administration (t_{max}) = 1.25 h [32]. It offers significant advantages over aspirin, indomethacin and pyrazolone derivatives, because many patients tolerate it much better [23]. It was derived from propionic acid in 1960s [1] as a non-selective inhibitor of enzyme cyclooxygenase (COX1 and COX2), which converts arachidonic acid to prostaglandins (mediators of fever and pain) and to thromboxane (stimulated production of blood clots) [31]. Therefore, it can be used to relieve pain, reduce fever and swelling [2]. Ibuprofen can be effectively used in the treatment of mild to moderate pain, but it is not recommended for the treatment of neuropathic pain [30]. Collins et al. [7] assessed the analgesic effect of ibuprofen on moderate-to-severe pain, comparing it with placebo and diclofenac. A single dose of 400 mg ibuprofen gave the best results in pain relief, placebo relieved pain in 12% of patients, 200 mg of ibuprofen helped 39% of patients and 400 mg had effect on 60% of patients. The effect similar to 400 mg of ibuprofen can be observed after using 50 mg of diclofenac.

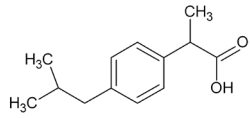

Figure 1. The chemical structure of ibuprofen

Ibuprofen can be easily found in the form of tablets, capsules, gels (5-10%), suppositories, solutions, syrups and suspensions. The recommended dose per person is 200 to 400 mg every 4 to 6 hours; a maximum daily dose is 1.2 g [26]. Orally administrated ibuprofen delayed analgesic action in many formulations, especially in the form of tablets [30]. Ibuprofen causes the smallest range of side effect among the non-selective NSAIDs. However, common side effects, which occur after taking ibuprofen are: diarrhea, dyspepsia, nausea, headaches, hypertension and hearing loss [9]. By combining L-arginine (amino acid) and the racemic ibuprofen, a highly soluble salt (ibuprofen arginate) can be obtained [30]. The L-arginate salt of ibuprofen can lead to a better analgesic effect and fewer side effects than racemic ibuprofen because arginine can reduce oxidative stress induced by ibuprofen and it is less toxic for the gastrointestinal tract [30].

CAFFEINE INFLUENCE ON NSAIDS

First clinical studies carried out in 1960s and 1970s did not show that caffeine can potentiate the analgesic effect of ibuprofen and other NSAIDs. Later, when new studies were performed, other authors provided data that caffeine enhances the analgesic effect of NSAIDs [34] and can inhibit the development of acute gastric mucosal injury caused by the use of ibuprofen [21].

Tavares and Sakata [37] investigated the analgesic effect of caffeine alone, but they were unable to confirm their assumptions. However, there were reports presenting synergistic effects of ibuprofen and caffeine in the treatment of pain [13]. In this way, the doses of NSAIDs can be reduced as well as the number of their side effects [12]. Lopez et al. [23] observed that co-administration of caffeine and ibuprofen improved the analgesic effect of ibuprofen in experimental models with laboratory animals.

There are several hypotheses on how caffeine can influence the NSAID's analgesic effect. It is known that caffeine does not modify the plasma level of ibuprofen and ibuprofen does not influence the bioavailability of caffeine [17]. Therefore, it is most likely that the antinociceptive effect caused by caffeine can be observed due to blockade of the peripheral pronociceptive effect of adenosine. A better mood can be observed because central nervous system and supraspinal noradrenergic pathways are activated [34, 35].

TABLETS

Low manufacturing costs, easy dosing and a possibility of modified drug release time make tablets the most commonly used solid dosage form [25]. The bioavailability of the active substance from the tablet depends on the rate of absorption in the gastrointestinal tract and the amount of drug, which enters the systemic circulation. The process

of tablet production by direct compression requires the content uniformity of the excipients and the drug [19].

Production technology of tablets containing ibuprofen and caffeine can be not easy because of poor compressible and mechanical properties of ibuprofen. It can be modified by milling, which significantly affects the flow and compressibility. The mechanical properties can be improved by co-crystallization of caffeine by either using calcium carbonate and sorbitol during wet granulation or by modification of the tablet surface by coating with highly bonding polymer such as PVP [28].

An example of a fast-created formulation of controlled release tablets containing ibuprofen and caffeine can be prepared using such excipients as tragacantha, polyethylene glycol 6000, and hydroxymethylcellulose, which may be a good alternative for hydroxypropyl methylcellulose [10]. For fast analysis, spectrophotometry can be used to determine ibuprofen and caffeine. Either alone or in combination, the simplicity and rapidity of the spectrophotometric method can be upgraded by chemometric calibration techniques in order to analyze the quality of a drug in multicomponent pharmaceutical drugs [20].

CAFFEINE AND IBUPROFEN FOR TREATMENT OF PAIN

McQuay et al. [27] compared analgesic effect of ibuprofen plus caffeine vs. ibuprofen after third molar surgery. Results obtained from 161 patients (range 16-53 years) showed that 200 mg of ibuprofen plus 100 mg of caffeine produced the best analgesia score, much better than 200 or 400 mg of ibuprofen. Adding 50 mg of caffeine to 200 mg of ibuprofen did not provide such a good result, while adding 200 mg of caffeine gave a better result than 400 mg of ibuprofen alone. Two patients who took 200 mg of ibuprofen plus 100 mg of caffeine had side effects. One had a headache and the other one felt faint. Other doses also caused minor side effects.

López et al. [23] assessed the influence of different doses of caffeine on analgesic effect of various doses of ibuprofen and placebo in male Wistar rats. The median effect dose (ED_{50}) of ibuprofen administered alone amounted to approximately 22.3 mg/kg, while combined with caffeine (ED_{50}) amounted to 17.8 mg/kg for ibuprofen and 9.2 mg/kg for caffeine. Results confirmed the previous thesis that caffeine can potentiate the analgesic effect of ibuprofen.

Dooley et al. [13] studied the influence of caffeine on ibuprofen in the treatment of headaches in children aged 7-15 years. The study was carried out in pediatric hospital on 12 patients. One group was treated with 100-400 mg of ibuprofen and 50-100 mg of caffeine. The other was treated with placebo and ibuprofen. The amount of the drug administrated depended on the body weight. The results were promising: 7 out of 12 patients observed faster relief after the co-administration of ibuprofen and caffeine.

Derry et al. [11] assessed the impact of a single dose of common analgesics such as ibuprofen, paracetamol, and acidum acetylsalicylicum plus caffeine comparing with the single dose of the analgesics alone on 7238 participants. In most studies paracetamol or ibuprofen were used with 100-130 mg of caffeine. Patients suffered headaches, postoperative dental pain and postpartum pain. About 20-25% of patients felt relieved after administration of NSAIDs plus caffeine comparing with 10-15% treated with NSAIDs only.

CONCLUSIONS

Every day the majority of people in the world drink coffee, tea, energy drinks and other products containing caffeine. A chronic intake of large doses of caffeine can lead to the physical dependence, tolerance and many side effects. However, small doses of caffeine can enhance the analgesic effect of ibuprofen, which was confirmed in many studies.

It has been shown that the dose of ibuprofen can be reduced thanks to the addition of caffeine, while the therapeutic effect of the drug remains the same. The positive impact of caffeine on analgesic effect of ibuprofen and other NSAIDs has been proved in the treatment of headaches in children. After third molar removal 200 mg of ibuprofen plus 100 mg of caffeine gave the best pain relief effect.

Ibuprofen is commonly used in the form of tablets as they are used in the treatment of mild to moderate pain. Combination of ibuprofen and caffeine also can be manufactured in the form of tablets as a new analgesic drug with fewer side effects and stronger analgesic effects than NSAIDs administered alone.

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